Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. N Engl J Med 2010;363:1693-703.

Appendix of contributors:
Massachusetts General Hospital

Marguerite H. Parkman
Natasha Isaac
Jennifer S. Temel
Julie Miller Batten
Aniruddha Ganguly
Georgiana Kuhlmann
Kristin Bergethon
Kathy Vernovsky
Beow Yeap
Leif Ellisen
Darrell Borger
Dora Dias-Santagata
Eugene Mark
Ultan McDermott
Anhthu Nguyen

Dana-Farber/Brigham and Women's Hospital Cancer Center

Scott Rodig
Charles Lee
Lucian Chirieac
Andrew Wolanski
James Cleary
Kristen Johnson
Caryn Kata
Tracy Bell
Kathleen Fiel
Kristie Stolgitis
Linda Pointon
Nick Mann
Fernanda Nery
Dongpo Cai

Beth Israel Deaconess Medical Center

Susumu Kobayashi
Myles Clancy

Peter MacCallum Cancer Centre

Stephen Fox
Alex Dobrovic
Toni-Maree Rogers
Allison Lamb
Jaclyn Bartlett

University of Colorado

S. Gail Eckhardt
Amanda Schubert
Courtney Scott
Stacy Grolnic
Wilbur A. Franklin

Seoul National University College of Medicine

Dong-Wan Kim
Se-Hoon Lee
Do youn Oh
Sae-Won Han
Hyunju Ryu

Memorial Sloan Kettering Cancer Center

Marc Ladanyi
William Pao
Katrina Watson
Lindsey Burgess
Linda Ahn
Mark Kris
Vincent Miller
Gregory Riely
M. Catherine Pietanza
Naiyer Rizvi
Christopher G. Azzoli
Mary Louise Keohan
David D'Adamo
Lee Krug

University of California, Irvine

Antonio Sanchez
Paula Goldfarb
Joni Dy

Pfizer

Joseph Prokop
Gina-Lee Emory
Paulina Selaru
Patricia Stephenson (Rho, Inc.)

Supplemental text:

ECOG Performance Status: 0 Fully active, able to carry on all pre-disease performance without restriction; 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

RECIST version 1.0 Tumor Assessment Criteria
At baseline, tumor lesions will be categorized as measurable or non-measurable (defined below).

All baseline evaluations will be performed as close as possible to the first day of study treatment and never more than 4 weeks before starting therapy.

Measurable Lesions

- Lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques or ≥1.0 cm with spiral CT scan.
- A tumor lesion that is situated in a previously irradiated area is eligible for measurable disease provided: 1) there has been documented disease progression in this site; 2) the criteria for measurability as outlined above are met; 3) this is not the only site of measurable disease.
- All measurements should be determined using a ruler, calipers or digital technology, and recorded on the CRF in metric notation.

Nonmeasurable Lesions

All other lesions, including small lesions (longest diameter <2.0 cm with conventional techniques or <1.0 cm with spiral CT) and truly nonmeasurable lesions. Truly nonmeasurable lesions include bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis or pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Documentation of Target and Nontarget Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and measured and recorded at baseline. Target lesions (measurable) should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as present or absent.

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Accepted methods of tumor assessment include:

Clinical examination: clinically detected lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest x-ray: lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI: CT and MRI are the best currently available and most reproducible methods of measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Ultrasound: should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and non-small cell lung nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy and Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully or widely validated. Utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

Tumor markers: tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered a complete clinical response.

Cytology and histology: the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

The following RECIST criteria will be the primary method utilized in this study for the assessment and reporting of tumor response data.

Complete Response (CR): Disappearance of all target and nontarget lesions, normalization of tumor marker levels, and no appearance of new lesions indicates complete response. Each of these must be documented on 2 occasions separated by at least 4 weeks.

Partial Response (PR): At least a 30% decrease in the sum of the LDs of target lesions (taking as reference the baseline sum), without progression of nontarget lesions and no appearance of new lesions indicates partial response. Each of these must be documented on 2 occasions separated by at least 4 weeks.

Stable Disease (SD): Neither PR or PD criteria are met.

Progressive Disease (PD): ≥20% increase in the sum of the LD of target lesions taking as references the smallest sum LD recorded since the treatment started, unequivocal progression of existing nontarget lesions, or the appearance of 1 or more new lesions. The occurrence of a pleural effusion or ascites is also considered PD if substantiated by cytologic investigation and not previously documented. Pathologic fracture or collapse of bone is not necessarily evidence of disease progression; however, new bone lesions not previously documented are considered PD.

In cases where procedures used to assess tumor size suggest tumor necrosis or intratumor bleeding coincident with an increase in size, a PET scan or ultrasound should be considered because it is important to be sure that increasing lesions are due to increased tumor growth and not necrosis or bleeding.

Determination of Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. For PD, taking as reference the smallest measurements recorded since treatment started. For CR and PR the best response assignment will depend on the achievement of both measurement and confirmation (at the minimum of 28 days) criteria. Stable disease rate will be defined as the percentage of patients with stable disease based on the total number of patients evaluable for response.

Determination of Best Overall Response			
Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR[a]	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR[b]	Non-PD	No	PR
SD[c]	Non-PD	No	SD
PD[d]	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] Complete response.
[b] Partial response.
[c] Stable disease.
[d] Progressive disease.

Reverse transcriptase polymerase chain reaction to determine EML4-ALK breakpoints:

RNA was extracted using the Agencourt Formapure method (Agencourt Biosciences, Beverly, MA), and reverse transcribed with using Superscript III cDNA synthesis kit (Invitrogen, Carlsbad, CA). A common primer to exon 20 of *ALK* was used along with primers to exons 6,13, and 18 of *EML4* in order to determine EML4-ALK breakpoints. *ALK* exon 20 reverse primer: (TGTCTAACTCGGGAGACTATGAAA). *EML4* forward primers: exon 6 (CCTTCAACACCCAAATTAATACC), exon 13 (TATGGAGCAAAACTACTGTAGAGC), exon 18 (CACACAGACGGGAATGAACA). PCR amplifications were performed in an Eppendorf Mastercycler Gradient (Eppendorf, Hamburg, Germany). PCR was conducted in a total volume of 20 μl containing 1X Platinum Taq PCR buffer, 200 μM dNTPs, 2.0 mM $MgCl_2$, 0.4 μM primers, 1.0 U of Platinum Taq polymerase (Invitrogen, Carlsbad, CA) with 40 ng of cDNA, using the following conditions: initial denaturation at 94°C for 5 min, followed by 40 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, and primer extension at 72°C for 1 minute and 30 seconds. Breakpoints were confirmed by Sanger sequencing of RT-PCR products, using the Big-Dye 1.1 sequencing kit (Life Technologies/Applied Biosystems, Foster City, CA).

Immunohistochemistry (IHC): was performed on FFPE specimens using the BenchMark XT automated tissue staining system (Ventana Medical Systems, Inc., Tucson, AZ) using validated protocols. Briefly, slides were deparaffinized and endogenous peroxidase activity was blocked by incubation with 3% H_2O_2. Heat-induced antigen retrieval was performed using the Ventana CC1 mild reagent (Ventana Medical Systems), a combination of ethylenediaminetetraacetic acid (EDTA) and boric acid in Tris buffer, and the process was carried out for 30-60 minutes. After treatment with 10% normal goat serum to block nonspecific protein binding, a primary rabbit monoclonal antibody against

ALK (Cell Signaling, Danvers, MA) was applied, followed by incubation with horseradish peroxidase-conjugated multimer antibody reagent (Igs; Ventana Medical Systems). The antigen-antibody reaction was visualized using diaminobenzidine as chromogen (UltraView, Ventana Medical Systems). Finally the slides were lightly counterstained with hematoxylin. Slides were evaluated for intensity (0 no staining; 1+ light staining; 2+ moderate staining; 3+ strong staining) and distribution of ALK immunostaining. Any IHC intensity greater than 0 is defined as IHC positive.

Supplemental Figure 1.
Schematic diagram of *EML4* and *ALK* genes, as well as representative fusion variants (listed by *EML4* exon breakpoints). Multiple breakpoints within a given exon have been reported, for instance exons 2a and 2b, and 6a and 6b (14,15). Encoded EML4 domains: CC=coiled coil; HELP=hydrophobic echinoderm microtubule-associated protein-like domain; WD= WD repeats. Encoded ALK domains: TM=transmembrane; Kinase=intracellular tyrosine kinase; Exon 20 breakpoint (dashed line).

Supplemental Figure 2.
Panels A,B,C: ^{18}FDG-PET, CT, and merged image, respectively, prior to initiation of crizotinib.
Panels D,E,F: ^{18}FDG-PET, CT, and merged image after 2 cycles of therapy.

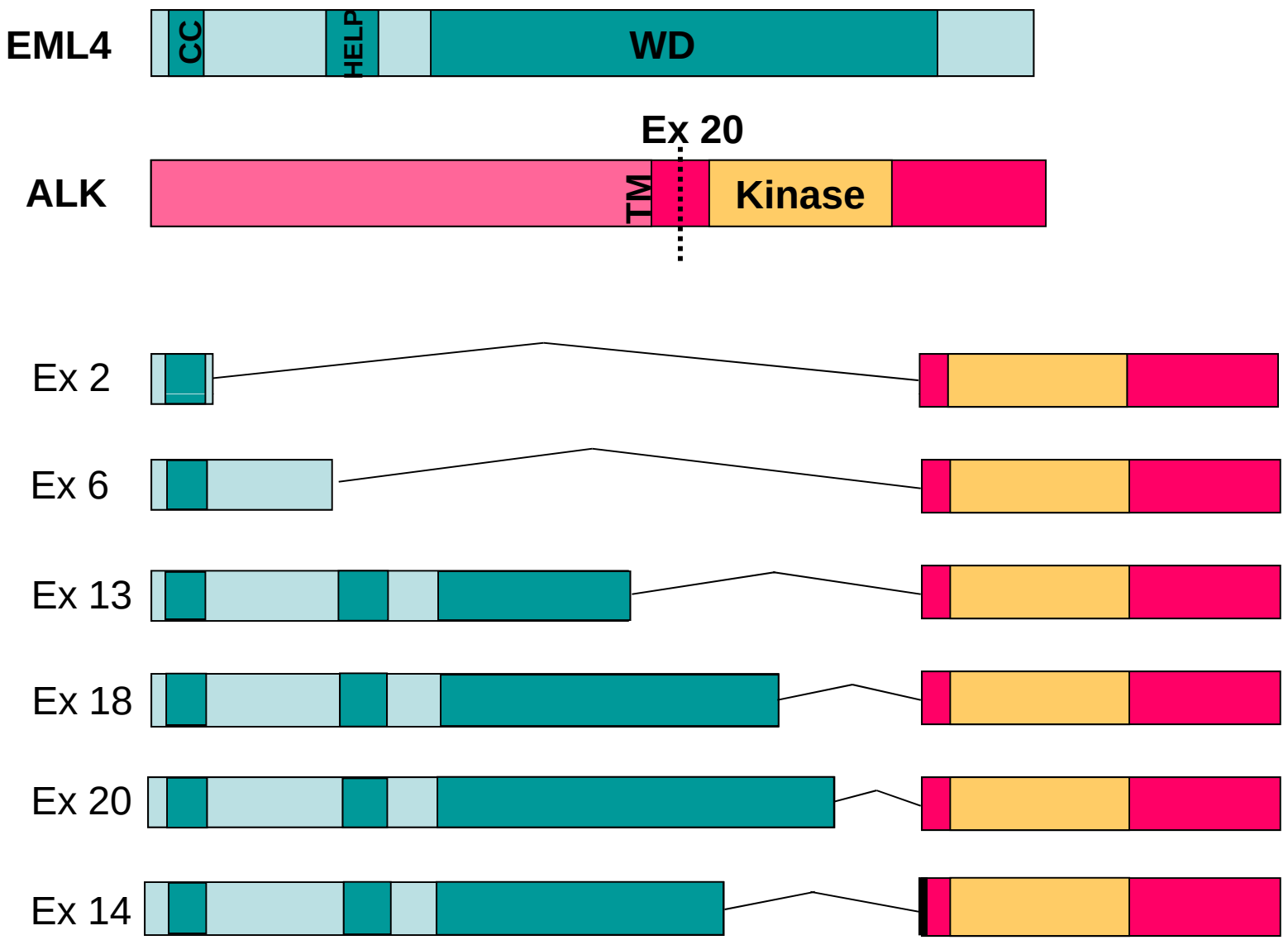
Supplemental Figure 3.
Panels A,B,C: ^{18}FLT-PET, CT, and merged image, respectively, prior to initiation of crizotinib.
Panels D,E,F: ^{18}FDG-PET, CT, and merged image after 1 cycle of therapy.

Supplemental Table 1
By World Health Organization (WHO) tumor classification criteria, the adenocarcinoma histologic subtype was solid with mucin in 48% of cases and mixed-type in 38% of cases.

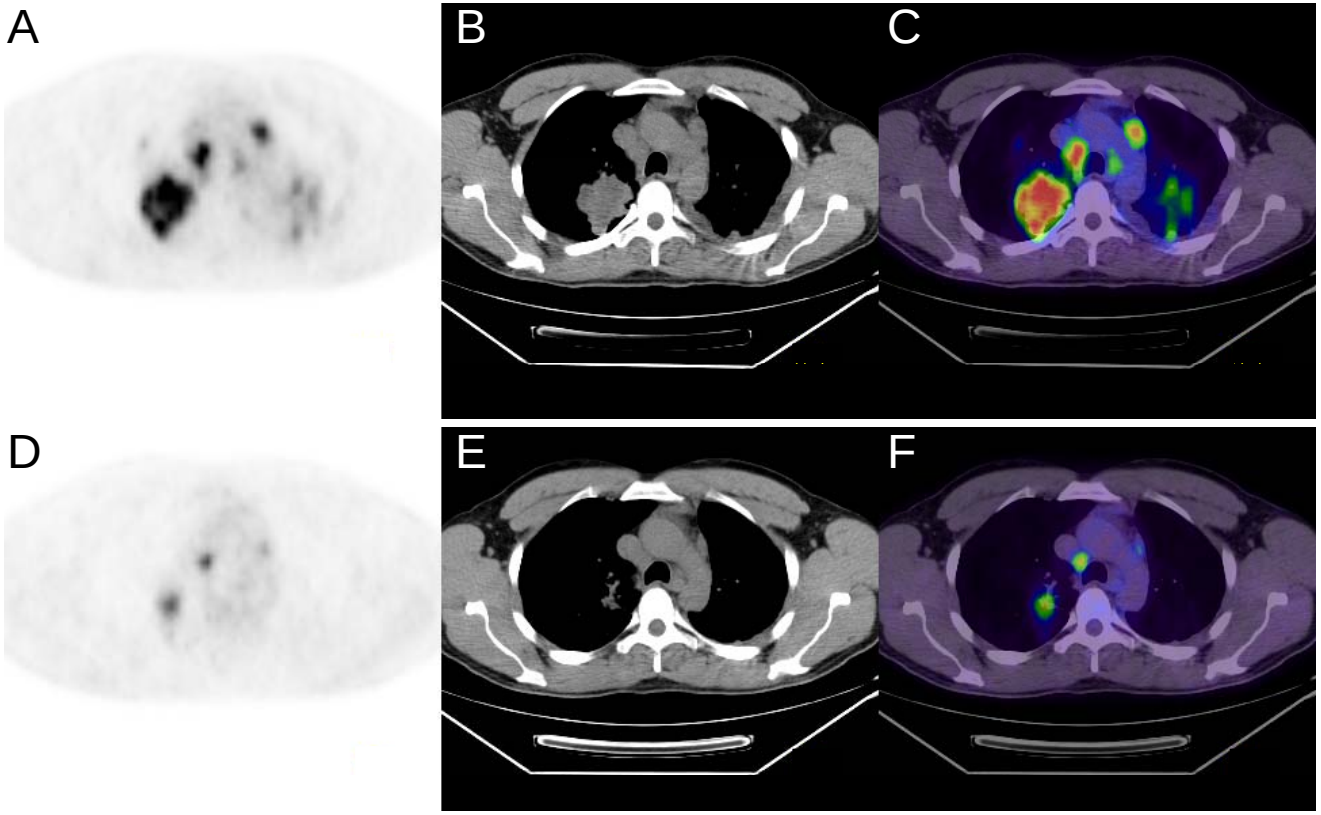
WHO histologic classification of NSCLC for *ALK* FISH-positive patients treated with crizotinib, listed by subject number as per Figure 2A. The percentage of signet ring cells is listed as >10%, <10% or 0. Other findings included several cases with numerous cells with dense eosinophilic cytoplasm, a feature not included in the WHO classification or in prior studies of ALK-positive NSCLC. *Adenocarcinoma diagnosis by report, slides not available (NA) for review to determine subtype.

Supplemental Table 2:
Prior treatment history for 82 patients receiving crizotinib, listed by subject number as per Figure 2A. Prior treatment status was not available in the database for 1 patient.

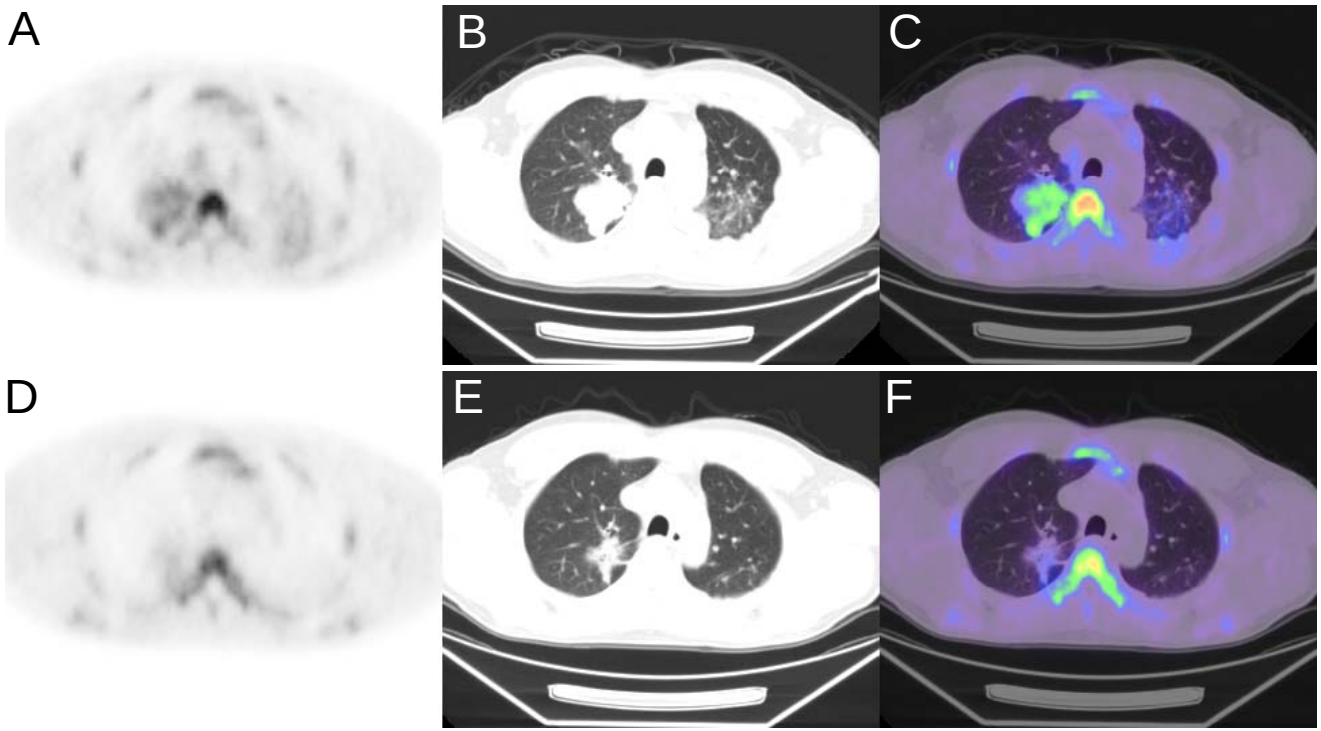
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemental Table 1

Subject #	Histology	Subtype	Signet ring cells	Other findings
1	Adenocarcinoma	Solid with mucin	<10%	
4	Adenocarcinoma/ squamous cell carcinoma	Solid with mucin (squamous histology sections not available for review)	<10%	
7	Adenocarcinoma*	NA		
16	Adenocarcinoma*	NA		
19	Adenocarcinoma	Solid with mucin	>10%	
21	Adenocarcinoma	Solid with mucin	>10%	
23	Adenocarcinoma*	NA		
25	Adenocarcinoma	BAC, mucinous	0	
27	Adenocarcinoma	Mixed, solid (90%), acinar (10%)	0	Dense eosinophilic cytoplasm
28	Adenocarcinoma*	NA		
29	Adenocarcinoma	Solid with mucin	>10%	
37	Adenocarcinoma	Solid with mucin	<10%	
38	Adenocarcinoma	Solid with mucin	>10%	
42	Adenocarcinoma	Mixed, 90% BAC (non-mucinous), 10% solid with mucin	>10%	
43	Adenocarcinoma	Solid with mucin	>10%	
45	Adenocarcinoma	Acinar	<10%	
51	Adenocarcinoma	Mixed, 70% solid with mucin, 30% acinar	>10%	
52	Adenocarcinoma	Solid with mucin	<10%	Dense eosinophilic cytoplasm
53	Adenocarcinoma	Mixed, 90% solid with mucin, 10% papillary	0	Dense eosinophilic cytoplasm
56	Adenocarcinoma	Mixed, 90% solid with mucin, 10% acinar	<10%	Dense eosinophilic cytoplasm
58	Adenocarcinoma	Mixed, 80% solid with mucin, 20% acinar	>10%	
59	Adenocarcinoma	Solid with mucin	>10%	
61	Adenocarcinoma	BAC, mucinous	<10%	
63	Adenocarcinoma*	NA		
66	Adenocarcinoma*	NA		
67	Adenocarcinoma	Mixed, solid with mucin 80%, acinar 20%	<10%	Dense eosinophilic cytoplasm
68	Adenocarcinoma	Mixed, acinar 60%, solid with mucin 20%, papillary 20%	<10%	
75	Adenocarcinoma	Mixed, BAC (80%), acinar (20%)	<10%	
79	Adenocarcinoma	Solid with mucin	<10%	Dense eosinophilic cytoplasm

Supplemental Table 2

Subject #	Regimen Number	Agent	Duration of treatment
1	1	INVESTIGATIONAL AGENT (XL-647)	168
2	1	CISPLATIN	296
2	1	GEMCITABINE	296
2	2	PEMETREXED	283
2	2	ERLOTINIB	283
2	3	RETASPIMYCIN	30
2	3	PACLITAXEL	30
2	4	DOCETAXEL	63
2	5	BEVACIZUMAB	105
2	5	PEMETREXED	105
3	1	CISPLATIN	110
3	1	PEMETREXED	110
3	2	PEMETREXED	44
3	3	AFLIBERCEPT OR PLACEBO	21
3	3	DOCETAXEL	21
3	4	BEVACIZUMAB	0
3	4	GEMCITABINE	7
4	1	CISPLATIN	25
4	1	CETUXIMAB	32
4	1	VINORELBINE	32
5	1	BEVACIZUMAB	219
5	1	CARBOPLATIN	128
5	1	PACLITAXEL	107
5	2	PEMETREXED	22
5	2	CETUXIMAB	22
6	1	BEVACIZUMAB	0
6	1	CARBOPLATIN	108
6	1	GEMCITABINE	96
6	1	PACLITAXEL	108
7	1	PEMETREXED	122
7	1	CISPLATIN	122
7	2	ERLOTINIB	14
7	3	PEMETREXED	20
8	1	BEVACIZUMAB	91
8	1	CARBOPLATIN	91
8	1	PACLITAXEL	91
8	2	BEVACIZUMAB	139
8	2	ERLOTINIB	139
8	3	PEMETREXED	335
8	3	BEVACIZUMAB	335
9	0		
10	1	PEMETREXED	62
10	1	CISPLATIN	62
11	1	CARBOPLATIN	22
11	1	DOCETAXEL	22
11	2	ERLOTINIB	6
11	3	PEMETREXED	107
11	3	CARBOPLATIN	107

Supplemental Table 2

11	4	PEMETREXED	224
11	5	DOCETAXEL	104
11	6	ERLOTINIB	88
11	7	CISPLATIN	7
11	7	GEMCITABINE	7
12	1	PEMETREXED	105
12	1	BEVACIZUMAB	105
12	1	CARBOPLATIN	105
13	1	CARBOPLATIN	66
13	1	PACLITAXEL	66
13	2	GEMCITABINE	196
13	2	VINORELBINE	196
14	1	CARBOPLATIN	31
14	1	PACLITAXEL	31
14	1	THALIDOMIDE	31
14	2	GEFITINIB	534
14	3	INVESTIGATIONAL AGENT: PF-00299804	NA
14	4	ERLOTINIB	0
15	Not reported		
16	1	ERLOTINIB	35
16	2	GEMCITABINE	42
16	3	BEVACIZUMAB	151
16	3	CARBOPLATIN	126
16	3	PACLITAXEL	126
16	4	PEMETREXED	203
16	5	BEVACIZUMAB (MAINTENANCE)	344
17	1	CARBOPLATIN	63
17	1	PACLITAXEL	63
17	2	PEMETREXED	88
17	2	CARBOPLATIN	88
18	1	CARBOPLATIN	20
18	1	GEMCITABINE	20
18	2	BEVACIZUMAB	211
18	3	ERLOTINIB	272
19	1	ERLOTINIB	64
20	1	BEVACIZUMAB	39
20	1	PACLITAXEL	39
20	1	PEMETREXED	39
21	1	CISPLATIN	92
21	1	GEMCITABINE	99
21	2	ERLOTINIB	36
22	1	CISPLATIN	20
22	1	PEMETREXED	20
22	2	CISPLATIN	40
22	2	ETOPOSIDE	40
23	1	PEMETREXED	0
23	1	CARBOPLATIN	NA
23	1	GEMCITABINE	60

Supplemental Table 2

23	1	ERLOTINIB	235
24	1	ERLOTINIB	122
24	2	CARBOPLATIN	120
24	2	PEMETREXED	120
24	3	DOCETAXEL	NA
24	4	ZOLEDRONIC ACID	NA
25	1	PEMETREXED	157
25	1	CISPLATIN	157
26	0		
27	0		
28	1	BEVACIZUMAB	144
28	1	CARBOPLATIN	122
28	1	PACLITAXEL	122
29	1	CISPLATIN	35
29	1	VINDESINE	35
29	2	CARBOPLATIN	45
29	2	PACLITAXEL	45
29	3	PAMIDRONATE	25
29	3	RENIN-ANGIOTENSIN SYSTEM AGENTS	25
30	1	BEVACIZUMAB	476
30	1	CARBOPLATIN	84
30	1	PACLITAXEL	84
31	1	CARBOPLATIN	0
31	1	GEMCITABINE	0
31	2	GEFITINIB	0
32	1	BEVACIZUMAB	85
32	1	CARBOPLATIN	85
32	1	PACLITAXEL	85
32	2	VINORELBINE	74
33	1	CARBOPLATIN	0
33	1	PACLITAXEL	0
33	2	ERLOTINIB	121
33	3	PEMETREXED	427
34	1	CISPLATIN	7
34	1	VINORELBINE	7
35	1	CARBOPLATIN/PACLITAXEL	63
36	1	CISPLATIN	40
36	1	VINORELBINE	40
37	1	CARBOPLATIN	30
37	1	GEMCITABINE	30
37	2	PEMETREXED	245
38	1	BEVACIZUMAB	NA
38	1	CARBOPLATIN	NA
38	1	PACLITAXEL	NA
39	1	INVESTIGATIONAL AGENT	NA
39	2	BEVACIZUMAB	104
39	2	ERLOTINIB	NA
39	3	CARBOPLATIN	68
39	3	PACLITAXEL	68
39	4	PEMETREXED	86

Supplemental Table 2

39	5	ERLOTINIB	29
39	6	SUNITINIB	105
39	7	GEMCITABINE	0
40	1	CISPLATIN	126
40	1	ERLOTINIB	126
40	1	PEMETREXED	126
40	2	ERLOTINIB	141
40	2	PEMETREXED	141
41	1	PEMETREXED	93
41	1	CARBOPLATIN	63
41	2	LOW DOSE CHEMOTHERAPY- IPT	10
42	1	CARBOPLATIN	212
42	1	GEMCITABINE	212
42	2	VANDETANIB	31
42	3	PEMETREXED	61
42	4	CARBOPLATIN	275
42	4	VINORELBINE	275
42	5	ERLOTINIB	122
42	6	DOCETAXEL	126
43	1	CISPLATIN	68
43	1	GEMCITABINE	68
43	2	DOCETAXEL	23
43	3	PEMETREXED	21
44	1	CISPLATIN	198
44	1	PACLITAXEL	198
44	2	GEMCITABINE	28
44	2	VINORELBINE	28
44	3	GEFITINIB	121
44	4	CISPLATIN	200
44	4	DOCETAXEL	200
44	5	PEMETREXED	572
45	1	BEVACIZUMAB	143
45	1	BORTEZOMIB	143
45	1	CARBOPLATIN	143
45	2	BEVACIZUMAB	151
45	3	PEMETREXED	18
45	4	BEVACIZUMAB	91
45	4	ERLOTINIB	73
46	1	CARBOPLATIN	69
46	1	PACLITAXEL	69
47	1	CARBOPLATIN	30
47	1	GEMCITABINE	30
47	2	DOCETAXEL	156
48	1	CISPLATIN	108
48	1	DOCETAXEL	108
48	1	ERLOTINIB	36
48	2	BEVACIZUMAB	243
48	2	PEMETREXED	364
48	3	GEMCITABINE	74
48	3	VINORELBINE	29

Supplemental Table 2

48	4	CARBOPLATIN	98
48	4	CETUXIMAB	98
48	4	PACLITAXEL	98
48	5	ERLOTINIB	38
48	6	SUNITINIB	0
49	1	CISPLATIN	24
49	1	PACLITAXEL	24
49	2	CARBOPLATIN	71
49	2	PACLITAXEL	71
49	3	ERLOTINIB	59
49	4	PEMETREXED	122
49	5	GEMCITABINE	138
49	6	VINORELBINE	56
49	7	DOCETAXEL	124
50	1	CARBOPLATIN	62
50	1	PACLITAXEL	62
51	1	CARBOPLATIN	23
51	1	GEMCITABINE	28
51	2	ERLOTINIB	71
51	3	CARBOPLATIN	20
51	3	PEMETREXED	90
52	1	GEFITINIB	19
52	2	CISPLATIN	31
52	2	TS-1	31
52	3	ERLOTINIB	168
52	4	DOCETAXEL	0
53	1	CARBOPLATIN	70
53	1	CISPLATIN	35
53	1	GEMCITABINE	147
53	2	VANDETANIB + PLACEBO	392
54	0		
55	1	CARBOPLATIN	68
55	1	PACLITAXEL	68
55	2	CISPLATIN	77
55	2	GEMCITABINE	77
55	3	ERLOTINIB	38
55	4	PEMETREXED	100
55	5	VINORELBINE	154
56	1	CISPLATIN	21
56	1	VINORELBINE	28
56	2	CARBOPLATIN	81
56	2	PACLITAXEL	81
56	3	CISPLATIN	15
56	3	GEMCITABINE	15
57	1	CISPLATIN	21
57	1	GEMCITABINE	21
58	1	CARBOPLATIN	NA
58	1	PACLITAXEL	NA
59	1	ERLOTINIB	29
59	2	CARBOPLATIN	118

Supplemental Table 2

59	2	PACLITAXEL	118
60	1	CARBOPLATIN	66
60	1	GEMCITABINE	66
60	2	ERLOTINIB	748
60	3	PF-00299804	256
60	4	ERLOTINIB	82
61	1	CISPLATIN	63
61	1	TAXOTERE	63
61	2	ERLOTINIB	60
62	1	CARBOPLATIN	66
62	1	PACLITAXEL	66
62	2	GEFITINIB	31
62	3	PEMETREXED	112
62	4	GEMCITABINE	133
63	1	CARBOPLATIN	144
63	1	GEMCITABINE	144
64	1	BEVACIZUMAB	NA
64	1	CARBOPLATIN	NA
64	1	PACLITAXEL	NA
65	0		NA
66	1	CARBOPLATIN	51
66	1	PACLITAXEL	51
66	2	CARBOPLATIN	140
66	2	PACLITAXEL	140
66	3	CISPLATIN	49
66	3	ETOPOSIDE	49
66	4	DOCETAXEL	4
66	5	GEFITINIB	380
66	6	PEMETREXED	63
66	6	BEVACIZUMAB	63
66	7	BEVACIZUMAB	350
67	1	CISPLATIN	76
67	1	GEMCITABINE	76
67	2	CISPLATIN	61
67	2	DOCETAXEL	61
67	3	CISPLATIN	76
67	3	TS-1	76
68	1	CISPLATIN	26
68	1	GEMCITABINE	26
68	2	DOCETAXEL	122
68	3	GEFITINIB	0
68	4	IFOSFAMIDE	137
68	4	MESNA	137
68	4	VINORELBINE	137
68	5	CARBOPLATIN	130
68	5	PACLITAXEL	130
68	6	PEMETREXED	277
68	7	IRINOTECAN	48
69	1	CARBOPLATIN	112
69	1	VINORELBINE	112

Supplemental Table 2

70	1	CISPLATIN	43
70	1	VINORELBINE	43
70	2	CARBOPLATIN	0
70	2	PACLITAXEL	0
71	1	CARBOPLATIN	63
71	1	PACLITAXEL	63
72	1	CISPLATIN	141
72	1	GEMCITABIN	141
72	2	GEFITINIB	14
72	3	PEMETREXED	108
72	4	VINORELBINE	161
73	1	CARBOPLATIN	28
73	1	PACLITAXEL	28
74	1	CARBOPLATIN	69
74	1	PACLITAXEL	69
74	2	ERLOTINIB OR PLACEBO	340
74	3	CISPLATIN	21
74	3	GEMCITABINE	21
74	4	GEFITINIB	210
75	1	CISPLATIN	113
75	1	VINORELBINE	113
76	1	BEVACIZUMAB	21
76	1	CARBOPLATIN	65
76	1	PACLITAXEL	65
76	2	BEVACIZUMAB	92
76	2	ERLOTINIB	92
76	3	PEMETREXED	63
76	3	SUNITINIB	63
76	4	PEMETREXED	246
76	4	SUNITINIB	350
77	1	CARBOPLATIN	67
77	1	PACLITAXEL	67
77	2	ERLOTINIB	112
77	3	PEMETREXED	40
78	1	BEVACIZUMAB	63
78	1	CARBOPLATIN	63
78	1	PACLITAXEL	63
78	2	ERLOTINIB	277
78	3	PEMETREXED	63
79	1	CISPLATIN	152
79	1	VINORELBINE	152
79	2	CISPLATIN	138
79	2	PACLITAXEL	138
79	3	GEFITINIB	61
79	4	GEMCITABINE	140
79	4	VINORELBINE	142
79	5	PEMETREXED	511
80	1	CETUXIMAB	127
80	1	CISPLATIN	113
80	1	VINORELBINE	120

Supplemental Table 2

81	1	GEFITINIB OR PLACEBO	58
81	2	CARBOPLATIN	63
81	2	CISPLATIN	63
81	2	PACLITAXEL	63
81	3	CARBOPLATIN	112
81	3	CISPLATIN	112
81	3	GEMCITABINE	112
81	4	ERLOTINIB	30
82	1	CARBOPLATIN	42
82	1	GEMCITABINE	49

* NA: Not available